

Cognitive Outcome After Off-Pump and On-Pump Coronary Artery Bypass Graft Surgery

A Randomized Trial

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CORONARY ARTERY BYPASS GRAFT (CABG) surgery with the use of cardiopulmonary bypass (CPB) is associated with significant cerebral morbidity, usually manifested as cognitive decline or stroke.¹ The incidence of cognitive decline ranges from 3% to 50%, depending on patient characteristics, definition of decline, and timing of neuropsychologic assessment.^{1,2} A recent pooled analysis of 6 comparable studies yielded a proportion of 23% of patients with cognitive decline 2 months after surgery.³ Although this degree of cognitive decline does not affect most patients in functional terms, a small proportion of patients with cognitive decline becomes sufficiently dis-

Context Coronary artery bypass graft (CABG) surgery is associated with a decline in cognitive function, which has largely been attributed to the use of cardiopulmonary bypass (on-pump procedures). Cardiac stabilizers facilitate CABG surgery without use of cardiopulmonary bypass (off-pump procedures) and should reduce the cognitive decline associated with on-pump procedures.

Objective To compare the effect of CABG surgery with (on-pump) and without (off-pump) cardiopulmonary bypass on cognitive outcome.

Design and Setting Randomized controlled trial conducted in the Netherlands of CABG surgery patients enrolled from March 1998 through August 2000, with 3- and 12-month follow-up.

Participants and Intervention Patients scheduled for their first CABG surgery (mean age, 61 years; n=281) were randomly assigned to off-pump surgery (n=142) or on-pump surgery (n=139).

Main Outcome Measures Cognitive outcome at 3 and 12 months, which was determined by psychologists (blinded for randomization) who administered 10 neuropsychological tests before and after surgery. Quality of life, stroke rate, and all-cause mortality at 3 and 12 months were secondary outcome measures.

Results Cognitive outcome could be determined at 3 months in 248 patients. Cognitive decline occurred in 21% in the off-pump group and 29% in the on-pump group (relative risk [RR], 0.65; 95% confidence interval [CI], 0.36-1.16; $P=.15$). The overall standardized change score (ie, improvement of cognitive performance) was 0.19 in the off-pump vs 0.13 in the on-pump group ($P=.03$). At 12 months, cognitive decline occurred in 30.8% in the off-pump group and 33.6% in the on-pump group (RR, 0.88; 95% CI, 0.52-1.49; $P=.69$). The overall standardized change score was 0.19 in the off-pump vs 0.12 in the on-pump group ($P=.09$). No statistically significant differences were observed between the on-pump and off-pump groups in quality of life, stroke rate, or all-cause mortality at 3 and 12 months.

Conclusion Patients who received their first CABG surgery without cardiopulmonary bypass had improved cognitive outcomes 3 months after the procedure, but the effects were limited and became negligible at 12 months.

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abled to prevent return to employment.¹ Perioperative stroke occurs in approximately 3% of the patients undergoing CABG surgery.^{1,4}

Cerebral morbidity after CABG surgery has largely been attributed to the use of CPB.¹ Cardiopulmonary bypass increases the permeability of the blood-

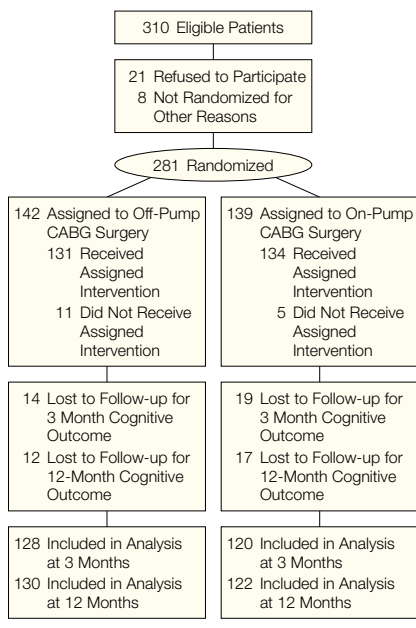
For editorial comment see p 1448.

Author Affiliations, Financial Disclosures, and Other Members of the Octopus Study Group are listed at the end of this article.

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Figure. Flow of Patients Throughout the Trial



CABG indicates coronary artery bypass graft.

Table 1. Patient Characteristics at Baseline

Characteristics, %	Off-Pump (n = 142)	On-Pump (n = 139)
Age, mean (SD), y	61.7 (9.2)	60.8 (8.8)
Education, mean (SD), y	9.3 (2.4)	9.7 (2.8)
Sex, male	66	71
Coronary artery disease		
1-Vessel disease	30	22
2-Vessel disease	50	50
3-Vessel disease	20	27
Peripheral vascular disease	7	13
Diabetes	9	17
History of stroke	4	3
Hypertension	40	44
Pulmonary disease	9	10

brain barrier and generates microemboli, which may affect cognitive function,⁵⁻⁷ and also requires cannulation and cross-clamping of the ascending aorta, which may induce atheromatous macroemboli causing stroke.⁸ Factors increasing the risk of cerebral morbidity include advanced age and prolonged time undergoing CPB.^{1,4} However, the assumption that CPB is the main cause of cerebral morbidity after CABG surgery has not been quantified in randomized trials of sufficient size. Two small trials showed conflicting results. One study (n=40)

demonstrated a marked improvement of cognitive outcome by using off-pump CABG surgery,⁵ while the other study (n=60) showed no improvement.⁶

Recently, cardiac stabilization devices were developed to facilitate CABG surgery on the beating heart (off-pump CABG), which allow immobilization and presentation of all sides of the beating heart,^{9,10} and for many patients complete revascularization can now be achieved without the use of CPB.¹⁰⁻¹² In a previous article,¹² we reported the clinical outcomes at 1 month after on-pump vs off-pump CABG surgery for patients in this clinical trial. In this study, we compared the effect of CABG surgery with and without CPB on cognitive outcome.

METHODS

Design and Patients

The design and methods of the Octopus trial have been described in detail.¹³ In brief, patients were eligible if referred for first-time isolated coronary bypass surgery and an off-pump procedure was deemed technically feasible. Patients were excluded in case of emergency or concomitant major surgery, Q-wave myocardial infarction in the last 6 weeks, or poor left ventricular function. Patients who were unlikely to complete 1-year follow-up, unable to give informed consent, or undergo neuropsychologic testing were excluded. There were no restrictions to age. Eligible patients were informed with a letter and invited to the outpatient clinic to receive additional information. After written informed consent was obtained, patients were randomly assigned by computerized block-randomization, over the telephone, to off-pump or on-pump CABG surgery. The block size varied from 8 to 20 patients and was unknown by the physicians who randomized the patients. The study was approved by the ethics committees of the 3 participating centers.

Between March 1998 and August 2000, 281 patients were enrolled, of whom 265 were treated according to randomization (FIGURE and TABLE 1).

Ten patients randomized to off-pump surgery underwent CABG with CPB because progression of symptoms required emergency surgery or because technical problems were encountered during the procedure. One other off-pump patient underwent coronary angioplasty. In 5 patients assigned to on-pump CABG surgery, an off-pump procedure was performed.

Outcome

The primary end point of the study was cognitive outcome at 3 months after surgery. Patients underwent a battery of 10 neuropsychologic tests 1 day before and 3 and 12 months after operation. The tests were administered in the participating hospitals by trained psychologists who were blinded to treatment allocation. Administration of the tests lasted approximately 100 minutes.

In accordance with the Statement of Consensus on Assessment of Neurobehavioral Outcomes after Cardiac Surgery,¹⁴ the battery included tests for motor skills, verbal memory capacity, and attention. In addition, tests were included to assess speed and capacity of working memory, visuospatial capacity, selective and sustained attention, and information processing. Each test yielded 1 or more variables, with different ranges per variable. Eleven main variables were chosen a priori to be used in the analyses. The cognitive domains that were covered, the tests, and the main variables¹³ are listed in TABLE 2. Cognitive decline was defined as a decrease in an individual's performance of at least 20% from baseline, in at least 20% (3) of the main variables.¹⁵ Patients who sustained a stroke were considered to have cognitive decline. To limit practice effects, 6 of the 10 tests were also administered 2 weeks before baseline assessment (pretest, Table 2) and, wherever possible, parallel forms of the tests were used in the consecutive assessments.

In addition to the primary analysis based on a dichotomous cognitive outcome, 2 additional analyses were performed, both including continuous cognitive outcome measures. The first

consisted of a direct comparison of the continuous test scores. To estimate the change in performance from baseline to 3 months after operation, a standardized change score (SCS) was calculated for each main variable in each patient by subtracting the preoperative score from the postoperative score and dividing the difference by the preoperative SD of that variable. If improved performance was reflected by a lower score (eg, in timed tasks), the directional data were reversed so that all improvements gave positive change scores. Per subject, the mean of the 11 SCSs was taken as a quantitative measure of the overall postoperative change in performance.^{16,17}

The second additional analysis of cognitive outcome included a factor analysis with orthogonal rotation, which was performed to minimize the overlap between the 11 main test variables and to facilitate interpretation.^{2,18} This reduced the data set to 4 independent factor scores, each representing a separate domain of cognitive function: (1) attention and visuospatial capacity; (2) verbal memory; (3) selective attention and motor capacity; and (4) working memory. The factor coefficients needed to calculate the factor scores at the vari-

ous time points were derived using the factor loadings and weights from the baseline cognitive data. Factor change scores were obtained by subtracting the baseline factor scores from the postoperative factor scores.

Secondary end points included identical measures of cognitive outcome at 12 months, differences in quality of life at 3 and 12 months, and stroke rate and all-cause mortality at 3 and 12 months. Health-related quality of life was assessed using 2 generic questionnaires. The EuroQol questionnaire generates a single index, ranging from -1 to +1, with -1 reflecting the worst imaginable quality of life and +1 reflecting the best imaginable quality of life.¹⁹ The Short Form-36 questionnaire comprises 8 different domains all ranging from 0 to 100. Higher scores indicate higher levels of functioning or well-being.²⁰ Stroke was defined as focal brain injury, detected by standard neurologic examination, persisting for more than 24 hours, and combined with an increase in functional deficit of at least 1 grade on the Rankin Scale.²¹

Treatment and Procedures

The goal of surgery was to obtain complete arterial revascularization. With the

exception of 2 emergency procedures, all operations were performed by cardiac surgeons experienced in both off-pump and on-pump bypass surgery. During off-pump procedures, the Octopus method⁹ (Octopus Device, Medtronic, Minneapolis, Minn) was used for stabilization of the target coronary artery.

The use of CPB requires full heparinization, which influenced the selection of anaesthetic technique. In the on-pump group, 99% of the patients received total intravenous anesthesia including high dose opioids, whereas in the off-pump group, 54% of the patients received thoracic epidural anesthesia combined with low-dose opioids. Cardiopulmonary bypass was managed according to the α -stat principle,²² with a minimal nasopharyngeal temperature of 32°C and a non-pulsatile perfusion of 2.0 to 2.4 L/m² per minute. The pump was primed with a crystalloid-colloid mixture. During rewarming, the maximal gradient between blood and water in the heat exchanger was 5°C with a maximal water temperature of 39°C. To reduce blood loss in the CPB group, blood was recollected using a suction cardiectomy reservoir, without filter or

Table 2. Cognitive Domains and Neuropsychologic Tests at Pretesting and Baseline*

Domain	Test	Main Variable	Median (10th-90th Percentiles)			
			Off-Pump		On-Pump	
			Pretest	Baseline	Pretest	Baseline
Verbal memory, learning	Rey Auditory Verbal Learning	Total score trial 1-5	37 (25-49)	36 (25-48)	35 (24-48)	36 (26-48)
Verbal memory, retrieval	Rey Auditory Verbal Learning	Delayed recall score	7 (4-11)	6 (3-9)	7 (3-10)	6 (3-10)
Motor capacity	Grooved Pegboard	Time dominant hand, s	107 (91-147)	106 (88-137)	107 (91-157)	104 (91-141)
Divided attention	Trail Making Test Parts A and B	Time trail B, s	97 (56-176)	83 (49-153)	91 (61-165)	84 (52-154)
Working memory speed	Sternberg Memory Comparison	Time 4-character chart, s	62 (42-89)	59 (43-88)	60 (45-86)	57 (43-87)
Visuospatial capacity	Line Orientation Test	Total score	25 (17-29)	24 (17-29)	24 (17-29)	24 (18-28)
Selective attention	Stroop Color Word Test	Time C - time B, s	48 (29-98)	43 (23-76)	46 (29-85)	40 (23-77)
Sustained attention	Continuous Performance Task	Mean reaction time, ms	...	544 (460-711)	...	544 (476-738)
Working memory	Self-ordering Tasks	Sum score	...	9 (5-16)	...	10 (6-17)
Visual working memory	Visuospatial Working Memory	Average distance, cm	...	0.4 (-0.3 to 1.5)	...	0.5 (-0.1 to 1.1)
Information processing	Symbol Digit Modalities Test	Total score	...	41 (25-55)	...	39 (26-53)

*Ellipses indicate not applicable. Pretest denotes cognitive performance 2 weeks before baseline assessment.

processing. In the off-pump group, a cell-saver was used.

Data Analysis

The sample size calculation was based on the assumptions that the incidence of cognitive decline at 3 months is 21% after on-pump CABG surgery³ and that a two-thirds reduction could be achieved using an off-pump technique. With the α error set at .05 and β error set at .10 (power of 90%), a total of 125 patients in each group were required, which was increased to 140 patients per group because a 10% loss to follow-up was anticipated.

Data were analyzed according to randomization. Incidences of cognitive decline and mortality were compared using Fisher exact test and the relative risk (RR) estimate with 95% confidence interval (CI). Odds ratios were used as a measure of RR. Continuous outcome measures were compared using the Wilcoxon nonparametric test. Differences in quality of life are presented as means with 95% CIs. For the cognitive outcome measures, multivariable regression models were used to adjust for possible baseline differences.

Missing Data

At 3 months, cognitive outcome and quality of life could be determined in 128 patients in the off-pump group and 120 patients in the on-pump group (Figure). Within these groups, 4 patients completed fewer neuropsychologic tests during postoperative assessment than at baseline. In the primary analysis (dichotomous cognitive outcome), these patients were considered to have a decreased performance of at least 20% on the missing tests (worst-case score).²³ To assess the effect of loss to follow-up, several additional analyses were performed. The baseline characteristics of the patients who completed cognitive follow-up were compared. A sensitivity analysis was performed in which the outcome, cognitive decline, was first assigned to the 19 on-pump CABG surgery patients without 3-month neuropsychologic testing, and then to the 14 off-pump patients without 3-month neu-

ropsychologic testing. Finally, missing cognitive data were imputed by means of linear regression modeling using SPSS version 10.0 (SPSS Inc, Chicago, Ill). Such modeling predicts the value of a missing variable by using all available cognitive and clinical data of that patient. Analyses were repeated with the completed data set.

RESULTS

Patient Population and Operation

Baseline characteristics of the patients, including preoperative cognitive test performance, were well balanced between the 2 groups (Tables 1 and 2). Patients in the off-pump group were on average 1 year older than the on-pump group and comprised slightly fewer men and patients with diabetes, peripheral vascular disease, and 3-vessel disease. The latter is reflected by the mean number of distal anastomoses, which was 2.4 in the off-pump and 2.6 in the on-pump group. For proximal anastomoses, aortic side clamps were used in 36% of the off-pump patients and 50% of the on-pump patients. In the on-pump group, time undergoing CPB averaged 66 minutes with 44 minutes cross-clamp time.

To assess the theoretical possibility of selection bias, the likelihood of the participants randomized to the off-pump group, which was influenced by the assignments of the previous patients, was entered in a logistic regression model. This variable appeared to be no determinant of cognitive outcome ($P = .99$). We also compared 21 baseline characteristics from off-pump patients who had a high likelihood of being randomized to off-pump with the baseline characteristics from on-pump patients with a low likelihood. No significant differences were observed in all the comparisons on the 21 baseline characteristics. Both analyses indicate that there was no selection bias (ie, the randomization sequence was well concealed).²⁴

Cognitive Outcome

The mean interval between operation and 3-month follow-up was 92 (SD, 17) days in the off-pump group and 96 (SD,

12) days in the on-pump group ($P = .06$). At 3 months after surgery, cognitive decline occurred in 21.1% of patients after off-pump CABG surgery and 29.2% after on-pump CABG surgery (RR, 0.65; 95% CI, 0.36-1.16; $P = .15$). The RR did not change after adjusting for baseline differences in age, sex, diabetes, peripheral vascular disease, and number of diseased vessels (RR, 0.65; 95% CI, 0.36-1.17; $P = .15$) or with adjustment for anesthetic technique (data not shown). Within the off-pump group, cognitive decline occurred in 22.7% of patients who received epidural anesthesia with low-dose opioids and 18.9% of patients who received high-dose opioids without epidural anesthesia ($P = .67$).

The results per neuropsychologic test variable are presented in TABLE 3. At 3 months, the patients in both groups improved on all 11 main variables. The overall postoperative change in performance (ie, overall improvement; mean of the 11 SCSs) was 0.19 SCS in the off-pump and 0.13 SCS in the on-pump group ($P = .03$). Adjustment for baseline differences did not change the difference between the groups.

The change in performance per cognitive domain, as calculated with factor analysis, is presented in TABLE 4. Patients improved on all domains from baseline to 3 months after surgery, but no statistically significant differences between the groups were present.

At 12 months, cognitive decline occurred in 30.8% of patients after off-pump CABG surgery and 33.6% after on-pump CABG surgery (RR, 0.88; 95% CI, 0.52-1.49; $P = .69$). The other analyses (Tables 3 and 4) also showed nonsignificant differences between the groups. An exception was the domain verbal memory (factor 2), which had improved twice as much in the off-pump group ($P = .01$). At 12 months, the overall change in cognitive performance was 0.19 SCS in the off-pump group and 0.12 SCS in the on-pump group ($P = .09$).

Missing Data

At 3 months, the cognitive outcome of 33 (12%) patients could not be determined and at 12 months the cognitive

data of 29 (10%) patients were not obtained. Reasons for not obtaining neuropsychological test data testing are summarized in TABLE 5. The 3-month sensitivity analysis yielded an RR of 0.37 (95% CI, 0.22-0.63) and 1.21 (95% CI, 0.71-2.05), which are the extremes that could be obtained if all patients had been available for 3-month follow-up. The baseline characteristics of the patients who were available for analysis of cognitive outcome were comparable to the baseline characteristics of the entire patient sample. Imputation of all missing data by means of linear regression increased the differences in cognitive decline between the 2 groups at 3 months. After imputation, the rate of cognitive de-

cline at 3 months was 19.0% in the off-pump group and 28.8% in the on-pump group (RR, 0.58; 95% CI, 0.33-1.02; $P = .07$), and the overall postoperative change in performance became 0.18 SCS and 0.13 SCS in the off-pump and on-pump groups, respectively ($P = .25$). After imputation, the RR for cognitive decline at 12 months was 0.90 (95% CI, 0.53-1.54; $P = .79$) and the overall postoperative change in performance became 0.20 SCS and 0.12 SCS in the off-pump and on-pump groups, respectively ($P = .05$).

Quality of Life

Both groups reported a marked improvement in overall quality of life at 3 months

as well as each of the 8 subdomains (TABLE 6). Within these domains, only bodily pain and general health perceptions improved further from 3 to 12 months. Direct comparison between the groups of the overall scores and scores per domain at 3 and 12 months revealed only nonsignificant differences.

Mortality and Stroke

At 3 months, 1 nonfatal stroke (perioperative) occurred in the off-pump group and 2 nonfatal strokes (1 perioperative) in the on-pump group. One off-pump patient died from gastrointestinal bleeding 49 days after CABG surgery and 1 on-pump patient died 58 days after perioperative myocardial infarction.

Table 3. Neuropsychologic Tests and Standardized Change Scores (SCSs) at 3 and 12 Months After Surgery*

Test	Median (10th-90th Percentiles)								P Value of Off-Pump vs On-Pump	
	Off-Pump				On-Pump				3 Months	12 Months
	3 Months		12 Months		3 Months		12 Months			
	Raw	Change	Raw	Change	Raw	Change	Raw	Change	3 Months	12 Months
Rey, total score	38 (24-49)	0.00	41 (27-53)	0.33	37 (23-51)	0.11	37 (28-53)	0.22	.59	.26
Rey, delayed recall	7 (3-11)	0.40	8 (5-12)	0.79	7 (2-11)	0.00	7 (3-11)	0.40	.13	.01
Grooved Pegboard	100 (86-134)	0.07	99 (85-130)	0.03	102 (88-124)	0.14	102 (90-135)	0.07	.78	.85
Trail Making Test part B	75 (50-137)	0.13	77 (45-137)	0.16	79 (50-137)	0.11	76 (50-134)	0.09	.33	.51
Sternberg Memory Comparison	56 (39-86)	0.18	57 (38-82)	0.12	59 (44-88)	0.06	58 (45-81)	0.03	.28	.19
Line Orientation Test	26 (19-29)	0.23	25 (19-30)	0.23	25 (19-29)	0.12	25 (19-29)	0.23	.31	.57
Stroop Color Word Test	39 (26-73)	0.41	43 (22-71)	0.08	37 (21-69)	0.12	40 (24-69)	0.00	.69	.50
Continuous Performance Task	536 (452-735)	0.11	544 (444-726)	0.04	521 (467-737)	0.09	526 (451-717)	0.08	.59	.25
Self-ordering Tasks	11 (6-17)	0.12	11 (6-17)	0.25	11 (6-17)	0.12	11 (5-16)	0.12	.61	.18
Visuospatial Working Memory	0.3 (-0.3 to 1.3)	0.08	0.5 (-0.3 to 1.5)	0.11	0.4 (-0.4 to 1.2)	0.23	0.4 (-0.4 to 1.2)	-0.04	.71	.56
Symbol Digit Modalities Test	45 (28-60)	0.27	42 (26-59)	0.09	42 (29-55)	0.18	41 (26-56)	0.18	.23	.64
Overall postoperative change (mean of the change scores)	...	0.19	...	0.19	...	0.13	...	0.12	.03	.09

*Change denotes standardized change score and reflects improved performance from baseline to 3 or 12 months after surgery. Ellipses indicate not applicable.

Table 4. Factor Change Score Analysis of Cognitive Function at 3 and 12 Months*

Cognitive Factor Score	Median (10th-90th Percentiles)				P Value of Off-Pump vs On-Pump	
	Off-Pump		On-Pump		3 Months	12 Months
	3 Months	12 Months	3 Months	12 Months		
Change in factor 1	0.21 (-0.46 to 0.80)	-0.02 (-0.67 to 0.75)	0.18 (-0.61 to 0.86)	0.14 (-0.58 to 0.71)	.76	.19
Change in factor 2	0.19 (-0.92 to 1.55)	0.53 (-0.64 to 1.70)	0.09 (-1.31 to 1.05)	0.18 (-0.79 to 1.40)	.19	.01
Change in factor 3	0.08 (-0.47 to 0.80)	-0.03 (-0.59 to 0.81)	0.08 (-0.49 to 0.71)	0.01 (-0.52 to 0.67)	.94	.97
Change in factor 4	0.08 (-0.67 to 0.73)	-0.04 (-0.67 to 0.84)	0.09 (-0.71 to 0.89)	-0.04 (-0.68 to 0.75)	.85	.67

*Positive values reflect improved performance from baseline to 3 or 12 months after surgery. Factor 1 denotes attention and visuospatial capacity; factor 2, verbal memory; factor 3, selective attention and motor capacity; and factor 4, working memory.

At 12 months, the mortality was 2 per group. In the off-pump group, 1 patient died from hepatic cancer 153 days after CABG surgery and in the on-pump group, 1 patient (who had had a previous stroke just prior to CABG surgery) died after a second 232 days after CABG surgery. The number of patients who had experienced stroke at 12 months remained 1 in the off-pump group and 2 in the on-pump group.

COMMENT

The use of CPB is generally regarded as the main cause of cognitive decline following heart surgery.¹ The present

study demonstrates limited improvement of cognitive outcome at 3 months in patients undergoing off-pump CABG surgery. The 29% incidence of cognitive decline after on-pump CABG surgery is consistent with previous, uncontrolled studies^{2,3} but the benefit of avoiding CPB was smaller than was anticipated. Moreover, at 12 months, the small differences between the groups had become negligible.

The present study is to our knowledge the largest randomized trial on cognitive outcome after off-pump and on-pump CABG surgery. Two other randomized studies on cognitive out-

come after CABG surgery were published recently. Age and extent of coronary disease of the participants of both studies were comparable with the present study. Diegeler et al⁵ administered the Syndrom Kurz Test to 40 patients and demonstrated a marked improvement of cognitive outcome after 7 days by using off-pump CABG surgery. Lloyd et al,⁶ in contrast, administered 7 tests from the Wechsler Memory Scale and Wechsler Adult Intelligence Scale to 60 patients and found no difference in cognitive function after 3 months.

Several reasons may be considered to explain the limited difference in cognitive outcome between the treatment groups observed in the present study. First, factors other than CPB may cause cognitive decline after CABG surgery. It is conceivable that undergoing anesthesia affects cognitive function, though in the present study no association was found between cognitive decline and type of anesthetic technique. Moller et al²⁵ demonstrated a 10% incidence of cognitive decline after noncardiac surgery, independent of regional or general anesthesia. These observations suggest that surgical trauma could be a source of cognitive decline.

Second, to minimize crossovers from off-pump to on-pump groups, stringent patient selection criteria were used.

Table 5. Reasons for Missing Neuropsychologic Assessment

Reason	3-Month Analysis		12-Month Analysis	
	Off-Pump	On-Pump	Off-Pump	On-Pump
Patient appeared to be unsuitable for neuropsychologic testing	1	1	1	1
Withdrawal immediately after randomization	0	3	0	3
Withdrawal after baseline assessment, but before surgery	2	4	2	4
Failure to administer baseline tests (logistic)	2	1	2	1
(Noncerebral) mortality at time of cognitive follow-up	1	1	2	1
Readmission to hospital or too ill for postoperative assessment	3	2	1	1
Failure to administer tests at time of cognitive follow-up (logistic)	1	0	1	0
Unable to come for follow-up (holiday or care for ill partners)	1	4	0	0
Not motivated for follow-up/withdrawal	3	3	3	6
Total No. of Patients With Missing Neuropsychologic Assessment	14	19	12	17

Table 6. Comparison of Quality of Life, Within and Between the Treatment Groups*

Domain	Off-Pump, Mean (SD)†			On-Pump, Mean (SD)†			Difference Between Off-Pump and On-Pump (95% Confidence Interval)	
	Baseline	3 Months	12 Months	Baseline	3 Months	12 Months	3 Months	12 Months
Physical functioning	52 (25)	82 (17)	80 (20)	52 (25)	81 (18)	81 (21)	1 (-4 to 6)	-1 (-6 to 4)
Role limitations due to physical health problems	23 (36)	62 (43)	69 (41)	23 (38)	56 (44)	74 (39)	6 (-5 to 17)	-5 (-15 to 5)
Bodily pain	62 (26)	80 (20)	82 (23)	61 (26)	77 (21)	84 (21)	3 (-2 to 8)	-2 (-7 to 3)
General health perceptions	56 (17)	71 (18)	67 (20)	54 (20)	68 (18)	66 (20)	3 (-2 to 8)	2 (-3 to 7)
Vitality	49 (23)	69 (19)	68 (20)	49 (24)	65 (20)	67 (18)	4 (-1 to 9)	1 (-4 to 6)
Social functioning	61 (30)	83 (22)	83 (22)	61 (30)	77 (24)	82 (21)	5 (-1 to 11)	0 (-5 to 6)
Role limitations due to emotional problems	51 (46)	79 (37)	79 (36)	53 (47)	76 (37)	84 (32)	3 (-7 to 13)	-5 (-13 to 4)
General mental health	66 (20)	80 (16)	78 (18)	67 (22)	78 (18)	78 (16)	2 (-2 to 6)	0 (-4 to 4)
Overall	0.64 (0.27)	0.86 (0.17)	0.82 (0.23)	0.65 (0.27)	0.83 (0.20)	0.86 (0.19)	0.03 (-0.02 to 0.07)	-0.04 (-0.09 to 0.02)

*Overall denotes overall quality of life.

†All differences within the groups between baseline and 3 months, and baseline and 12 months: $P < .01$ by the Wilcoxon signed rank test.

This has resulted in a relatively young group of patients (mean, 61 years) with less advanced coronary artery disease and limited comorbidity. The effects of an off-pump technique may be more marked in older patients, patients with more extensive coronary artery and aortic disease, and patients with substantial comorbidity.^{1,4,26}

Third, the off-pump technique may be a new source of cognitive decline. Exposure of the posterior cardiac wall frequently leads to transient episodes of elevated central venous pressure and concurrent decreased systemic blood pressure, resulting in a decreased cerebral perfusion pressure.²⁷

Fourth, improved cognitive outcome by using an off-pump technique may only become more clear in the long term. In a recent long-term follow-up study by Newman et al,² cognitive decline was found in 24% of the patients 6 months after on-pump CABG surgery, which increased to 42% after 5 years. The present study demonstrated an increasing incidence of cognitive decline from 3 to 12 months, but the difference in cognitive decline observed earlier between patients in the on-pump group and the off-pump group decreased.

A final explanation involves the definition of cognitive decline (20% decrease in performance in 20% of the variables), which appears to have limited precision. Although this definition has been reported to be sensitive and reliable,^{15,28,29} the cut-off value may be within the range of an individual's natural fluctuations in performance. Recently, the International Study of Post-Operative Cognitive Dysfunction group applied an almost similar definition to 176 volunteers undergoing 5 neuropsychologic tests.³⁰ After 3 months, 25% of the volunteers were identified as having cognitive decline. Therefore, it is likely that the true incidence of cognitive decline after CABG surgery is lower than generally assumed.³⁰ Moreover, measurement errors may have diluted the difference in cognitive decline found in the present study. Because of the methodological difficulties associated

with defining cognitive outcome at the individual patient level, we regard the analysis based on comparison of the continuous neuropsychologic test scores more reliable than the analysis based on the dichotomous outcome measure.

The present study has several limitations, including single blinding and a 12% loss to follow-up. It is unlikely, however, that the differences in cognitive outcome found between the groups were caused by loss to follow-up. Both the drop-out rate and the baseline characteristics of the remaining patients were largely similar across the groups. Adjustments for small inequalities in baseline characteristics did not affect the results. Imputation of cognitive data for the patients that were lost to follow-up increased the difference in cognitive decline between the groups. Only a small number of the patients in whom cognitive outcome could not be determined lost motivation for cognitive follow-up after their surgery. A relation between loss to follow-up and cognitive outcome may therefore be present in only a very small proportion of the patients. In addition, the sample size calculation was based on achieving a two-thirds reduction in cognitive decline at 3 months. Thus, a more modest benefit in reducing cognitive decline cannot be excluded and would need to be evaluated in larger randomized trials.

We conclude that patients who received their first CABG surgery without CPB had improved cognitive outcomes 3 months after the procedure, but the effects were limited and became negligible at 12 months.

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invention is commercialized. This applies to Drs Borst and Jansen. Dr Borst is a consultant with Medtronic and Dr Jansen is a member of its scientific advisory board. Medtronic has not been involved in the current study nor received any draft manuscript prior to publication.

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Two things fill my mind with ever-increasing wonder and awe: The starry heavens above me and the moral law within me.

—Immanuel Kant (1724-1804)